

D E C L A R A T I O N

In the matter of the patent application, I, Tetsuya KATO of c/o Minase Research Institute, Ono Pharmaceutical Co., Ltd., 1-1, Sakurai 3-chome, Shimamoto-cho, Mishima-gun, OSAKA, JAPAN, do hereby solemnly and sincerely declare as follows:

1. That I am a translator of Ono Pharmaceutical Co. Ltd., of 1-5, Doshomachi 2-chome, Chuo-ku, Osaka-city, OSAKA, JAPAN.
2. That I well understand the Japanese and the English language.
3. That attached hereto is full, true and faithful translation of certified copy of the Application for patent filed in Japan, on 27th February, 1997 under the number Heisei 9-043143, made by me, Tetsuya KATO on the 26th day of August, 1999.

And I make this solemn declaration conscientiously believing the same to be true and correct.

Dated this 27th day of August, 1999.


Tetsuya Kato

Translation:

Patent Office
Japanese Government

This is to certify that the annexed is a true copy of the following application
as filed this Office.

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Title of the Invention:

A novel polypeptide, a method of producing it, a DNA encoding it,
a vector containing it, a host cell transformed with the vector,
an antibody of the peptide, a pharmaceutical composition
containing the polypeptide or the antibody

Number of claims: 10

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Title of the Invention:

A novel polypeptide, a method of producing it, a DNA encoding it, a vector containing it, a host cell transformed with the vector, an antibody of the peptide, a pharmaceutical composition containing the polypeptide or the antibody

Claims:

1. Substantially purified form of the polypeptide that comprising the amino-acid sequence shown in SEQ ID NO. 1 or 5, homologue thereof, fragment thereof or homologue of the fragment.
2. A polypeptide according to claim 1 that comprising the amino-acid sequence shown in SEQ ID NO. 1 or 5.
3. A cDNA encoding the polypeptide according to claim 1.
4. A cDNA according to claim 3 that comprising the nucleotide sequence shown in SEQ ID NO. 2 or 6 or a fragment cDNA selectively hybridized to the cDNA.
5. A cDNA according to claim 3 that comprising the nucleotide sequence shown in SEQ ID NO. 3 or 8 or a fragment cDNA selectively hybridized to the cDNA.
6. A replication or expression vector carrying the cDNA according to claim 3 to 5.
7. A host cell transformed with the replication or expression vector according to claim 6.
8. A method for producing the polypeptide according to claim 1 or 2 which comprises culturing a host cell according to claim 7 under a condition effective to express the polypeptide according to claim 1 or 2.

9. A monoclonal or polyclonal antibody against the polypeptide according to claim 1 or 2.

10. A pharmaceutical composition containing the polypeptide according to claim 1 or 2 or the antibody according to claim 9, in association with pharmaceutically acceptable diluent and/or carrier.

Detailed Description of the Invention

Technical Field of the Invention

The invention is related to novel polypeptides produced by a certain human stromal cell line and DNAs encoding the said polypeptides.

More particularly, the invention is related to novel polypeptides named to OAF065 α and OAF065 α (called them OAF065s hereafter), a process for the preparation them, DNAs encoding the said polypeptides, a vector containing the polypeptide, a host cell transformed by the vector, antibody of the said polypeptide, a pharmaceutical composition containing the polypeptide or antibody.

Background of the Invention

It is known that bone marrow stromal cells form bone marrow micro environment of immunologic, hematopoietic system etc, and they produce and secret essential factors to induce of proliferation and differentiation of stem cells, e.g. IL-7, SCF, IL-11, M-CSF, G-CSF, GM-CSF, IL-6, TGF- α , LIF etc. It is also made clear that a certain bone marrow stromal cells are related to bone metabolism (Kenneth Dorshkind Annu. Rev. Immunol. 8, 111-137. 1990). However, roles of stromal cell are not reconstituted completely from only isolated factors yet. It may suggest that existence of any factors which are not isolated yet.

Purpose of the Invention

The present inventors have directed their attention to this point and energetic research has been carried out in order to find novel factors

(polypeptides) especially secretory and membrane protein which are generated by a certain stromal cells.

Until now, when a man skilled in the art intends to obtain a particular polypeptide or a DNA encoding it, he generally utilizes methods by confirming an intended biological activity in a tissue or in a cell medium, isolating and purifying the polypeptide and then cloning a gene or methods by "expression-cloning" with the guidance of the biological activity.

However, physiologically active polypeptides in living body have often many kinds of activities. Therefore, it is increasing that after a gene is cloned, the gene is found to be identical to that encoding a polypeptide already known. Generally bone marrow stromal cell generates only a very slight amount of a factor and it makes difficult to isolate and to purify the factor and to confirm its biological activity.

Recent rapid developments in techniques for constructing cDNAs and sequencing techniques have made it possible to quickly sequence a large amount of cDNAs. By utilizing these techniques, a process, which comprises constructing cDNAs at random, identifying the nucleotide sequences thereof, expressing novel polypeptides encoded by them, is now in progress. Although this process is advantageous in that a gene can be cloned and information regarding its nucleotide sequence can be obtained without any biochemical or genetic analysis, the target gene can be discovered thereby only accidentally in many cases.

The present inventors have studied cloning method of genes coding proliferation and/or differentiation factors functioning in hematopoietic systems and immune systems. Focusing their attention on the fact that most of the secretory

proteins such as proliferation and/or differentiation factors (for example various cytokines) and membrane proteins such as receptors thereof (hereafter these proteins will be referred to generally as secretory proteins and the like) have sequences called signal peptides in the N-termini, the inventors conducted extensive studies on a process for efficiently and selectively cloning a gene coding for a signal peptide. Finally, we have successfully invented a screening method for cDNAs having sequence encoding signal peptides, we called the method as signal sequence trap (SST) (See Japanese Patent Application No. 6-13951). We also developed yeast SST method on the same concept. By the method using yeast, genes including sequence encoding signal peptide can be identified more easily and effectively (See USP No. 5,536,637).

By using SST method, the present inventors achieved to find novel membrane proteins produced by bone marrow stromal cell and DNAs encoding them, and we then completed the invention.

The polypeptide OAF065s of the invention are not known one, when amino acid sequences of the polypeptide was compared by a computer to all known sequences in data base of Swiss Prot Release 33.

It was found out that the polypeptides of the invention are type-I membrane protein and they have extracellular Cys rich region which commonly exists in the receptor family of Tumor necrosis factor (TNF) (See Fig. 1). So it was suggested that the polypeptides of the invention are novel membrane proteins which belong to TNF receptor family.

Construction of the Invention

The invention provides:

- 1) a polypeptide comprising an amino acid sequence shown in SEQ ID NO. 1 or NO. 5,
- 2) a DNA encoding the polypeptides described above (1),
- 3) a DNA comprising a nucleotide sequence shown in SEQ ID NO. 2 or NO. 6,
- 4) a DNA comprising a nucleotide sequence shown in SEQ ID NO. 3 or NO. 7.

More particularly, the invention is concerned with a polypeptide comprising amino acid sequence shown in SEQ ID NO. 1 or 5 in substantially purified form, a homologue thereof, a fragment of the sequence and a homologue of the fragment.

Further, the invention is concerned with DNAs encoding the above peptides. More particularly the invention is provided DNAs comprising nucleotide sequence shown in SEQ ID NO. 2, 3, 6 or 7, and DNA containing a fragment which is selectively hybridizing to the DNA comprising nucleotide sequence shown in SEQ ID NO. 2, 3, 6, or 7.

A polypeptide comprising amino acid sequence shown in SEQ ID NO. 1 or 5 in substantially purified form will generally comprise the polypeptide in a preparation in which more than 90%, e.g. 95%, 98% or 99% of the polypeptide in the preparation is that of the SEQ ID NO. 1 or 5.

A homologue of polypeptide comprising amino acid sequence shown in SEQ ID NO. 1 or 5 will be generally at least 70%, preferably at least 80 or 90% and more preferably at least 95% homologous to the polypeptide comprising amino acid

sequence shown in SEQ ID NO. 1 over a region of at least 20, preferably at least 30, for instance 40, 60 or 100 more contiguous amino acids. Such a polypeptide homologue will be referred to a polypeptide of the invention.

Generally, a fragment of polypeptide comprising amino acid sequence shown in SEQ ID NO. 1 or 5 or its homologues will be at least 10, preferably at least 15, for example 20, 25, 30, 40, 50 or 60 amino acids in length, and are also referred to by the term "a polypeptide of the invention".

A DNA capable of selectively hybridizing to the DNA comprising nucleotide sequence shown in SEQ ID NO. 2, 3, 6 or 7 will be generally at least 70%, preferably at least 80 or 90% and more preferably at least 95% homologous to the DNA comprising nucleotide sequence shown in SEQ ID NO. 2, 3, 6 or 7 over a region of at least 20, preferably at least 30, for instance 40, 60 or 100 or more contiguous nucleotides. Such DNA will be referred to "a cDNA of the invention".

Fragments of the DNA comprising nucleotide sequence shown in SEQ ID NO. 2, 3, 6 or 7 will be at least 10, preferably at least 15, for example 20, 25, 30 or 40 nucleotides in length, and will be also referred to "a DNA of the invention" as used herein.

A further embodiment of the invention provides replication and expression vectors carrying DNA of the invention. The vectors may be, for example, plasmid, virus or phage vectors provided with an origin of replication, optionally a promoter for the expression of the said DNA and optionally a regulator of the promoter. The vector may contain one or more selectable marker genes, for example a ampicillin resistance gene. The vector may be used in vitro, for example of the production of RNA corresponding to the cDNA, or used to transfect or transfect a host cell.

A further embodiment of the invention provides host cells transformed with the vectors for the replication and expression of the DNA of the invention, including the DNA SEQ ID NO. 2, 3, 6 or 7 or the open reading frame thereof. The cells will be chosen to be compatible with the vector and may for example be bacterial, yeast, insect or mammalian.

A further embodiment of the invention provides a method of producing a polypeptide which comprises culturing host cells of the invention under conditions effective to express a polypeptide of the invention. Preferably, in addition, such a method is carried out under conditions in which the polypeptide of the invention is expressed and then produced from the host cells.

DNA of the invention may also be inserted into the vectors described above in an antisense orientation in order to provide for the production of antisense RNA. Such antisense RNA may be used in a method of controlling the levels of a polypeptide of the invention in a cell.

The invention also provides monoclonal or polyclonal antibodies against a polypeptide of the invention. The invention further provides a process for the production of monoclonal or polyclonal antibodies to the polypeptides of the invention. Monoclonal antibodies may be prepared by common hybridoma technology using polypeptides of the invention or fragments thereof, as an immunogen. Polyclonal antibodies may also be prepared by common means which comprise inoculating host animals, for example a rat or a rabbit, with polypeptides of the invention and recovering immune serum.

The invention also provides pharmaceutical compositions containing a polypeptide of the invention, or an antibody thereof, in association with a

pharmaceutically acceptable diluent and/or carrier.

The polypeptide of the invention includes that which a part of their amino acid sequence is lacking (e.g., a polypeptide comprised of the only essential sequence for revealing a biological activity in an amino acid sequence shown in SEQ ID NO.1), that which a part of their amino acid sequence is replaced by other amino acids (e.g., those replaced by an amino acid having a similar property) and that which other amino acids are added or inserted into a part of their amino acid sequence, as well as those comprising the amino acid sequence shown in SEQ ID NO. 1 or 5.

As known well, there are one to six kinds of codon as that encoding one amino acid (for example, one kind of codon for Methioine (Met), and six kinds of codon for leucine (Leu) are known). Accordingly, the nucleotide sequence of DNA can be changed in order to encode the polypeptide having the same amino acid sequence.

The DNA of the invention, specified in (2) includes a group of every nucleotide sequences encoding polypeptides (1) shown in SEQ ID NO. 1 or 5. There is a probability that yield of a polypeptide is improved by changing a nucleotide sequence.

The DNA specified in (3) is the embodiment of the DNA shown in (2), and indicate the sequence of natural form.

The DNA shown in (4) indicates the sequence of the DNA specified in (3) with natural non-translational region.

cDNA carrying nucleotide sequence shown in SEQ ID NO. 3 is prepared by the following method:

Brief description of Yeast SST method (see USP No. 5,536,637) is as follows.

Yeast such as *Saccharomyces cerevisiae* should secrete invertase into the medium in order to take sucrose or raffinose as a source of energy or carbon (Invertase is an enzyme to cleave raffinose into sucrose and melibiose, sucrose into fructose and glucose.). It is known that many known mammalian signal sequence make yeast secrete its invertase. From these knowledge, SST method was developed as a screening method to find novel signal sequence which make it possible can to secrete yeast invertase from mammalian cDNA library. SST method uses yeast growth on raffinose medium as a marker. Non-secretory type invertase gene SUC2 (GENBANK Accession No. V 01311) lacking initiation codon ATG was inserted to yeast expression vector to prepare yeast SST vector pSUC2. In this expression vector, ADH promoter, ADH terminator (both were derived from AAH5 plasmid (Gammerer, Methods in Enzymol. 101, 192-201, 1983)), 2 μ ori (as a yeast replication origin), TRP1 (as a yeast selective marker), ColE1 ori (as a E. Coli replication origin) and ampicillin resistance gene (as a drug resistance marker) were inserted. Mammalian cDNA was inserted into the upstream of SUC2 gene to prepare yeast SST cDNA library. Yeast lacking secretory type invertase, was transformed with this library. If inserted mammalian cDNA encodes a signal peptide, yeast could be survive in raffinose medium as a result of restoring secretion of invertase. Only to culture yeast colonies, prepare plasmids and determine the nucleotide sequence of the insert cDNAs, it is possible to identify novel signal peptide rapidly and easily.

Preparation of yeast SST cDNA library is as follows:

- (1) mRNA is isolated from the targeted cells, second-strand synthesis is performed

by using random primer with certain restriction enzyme (enzyme I) recognition site,
(2) double-strand cDNA is ligated to adapter containing certain restriction endonuclease (enzyme II) recognition site, differ from enzyme I, digested with enzyme I and fractionated in a appropriate size,
(3) obtained cDNA fragment is inserted into yeast expression vector on the upstream region of invertase gene which signal peptide is deleted and the library was transformed.

Detailed description of each step is as follows:

(1) mRNA is isolated from mammalian organs and cell lines stimulate them with appropriate stimulator if necessary) by known methods (Molecular Cloning(Sambrook, J., Fritsch, E. F. and Maniatis, T., Cold Spring Harbor Laboratory Press, 1989) or Current Protocol in Molecular Biology (F. M. Ausubel et al, John Wiley & Sons, Inc.) if not remark especially).

HAS303 (human bone marrow stromal cell line: provide from Professor Keisuke Sotoyama, Dr. Makoto Aizawa of Tokyo Medical College, 1st medicine; see J. Cell. Physiol., 148, 245-251, 1991 and Experimental Hematol., 22, 482-487, 1994) and HUVEC (human umbilical vein cord endothelial cell: ATCC No. CRL-1730) are chosen as a tissue source. Double-strand cDNA synthesis using random primer is performed by known methods.

Any sites may be used as restriction endonuclease recognition site I which is linked to adapter and restriction endonuclease recognition site II which is used in step (2), if both sites are different each other. Preferably, EcoRI is used as enzyme I and XhoI as enzyme II.

In step (2), cDNA is created blunt-ends with T4 DNA polymerase, ligated

enzyme II adapter and digested with enzyme I. Fragment cDNA is analyzed with agarose-gel electrophoresis (AGE) and is selected cDNA fraction ranging in size from 300 to 800 bp. As mentioned above, any enzyme may be used as enzyme II if it is not same the enzyme I.

In step (3), cDNA fragment obtained in step (2) is inserted into yeast expression vector on the upstream region of invertase gene which signal peptide is deleted. *E. coli* transformed with the expression vector. Many vectors are known as yeast expression plasmid vector. For example, YEp24 is also functioned in *E. Coli*. Preferably pSUC2 as described above is used.

Many host *E. Coli* strains are known for transformation, preferably DH10B competent cell is used. Any known transformation method is available, preferably it is performed by electroporation method. Transformant is cultured by conventional methods to obtain cDNA library for yeast SST method.

However not every All of the clones do not contain cDNA fragment. Further all of the gene fragments do not encode unknown signal peptides. It is therefore necessary to screen a gene fragment encoding for an unknown signal peptide from the library.

Therefore, screening of fragments containing a sequence encoding an appropriate signal peptide is performed by transformation of the cDNA library into *Saccharomyces cerevisiae* (e.g. Y1455 strain) which lack invertase (it may be prepared by known methods.). Transformation of yeast is performed by known methods, e.g. lithium acetate method. Transformant is cultured in a selective medium, then transferred to a medium containing raffinose as a carbon source. Survival colonies are selected and then prepared plasmid. Survival colonies on a raffinose-medium

indicates that some signal peptide of secretory protein was inserted to this clone.

Isolated positive clones is determined the nucleotide sequence. As to a cDNA encodes unknown protein, full-length clone may be isolated by using cDNA fragment as a probe and then determined to obtain full-length nucleotide sequence. These manipulation is performed by known methods.

Once the nucleotide sequences shown in SEQ ID NO. 2, 3, 6 or 7 are determined partially or preferably fully, it is possible to obtain DNA encode mammalian protein itself, homologue or subset. cDNA library or mRNA derived from mammals was screened by PCR with any synthesized oligonucleotide primers or by hybridization with any fragment as a probe. It is possible to obtain DNA encodes other mammalian homologue protein from other mammalian cDNA or genome library.

If a cDNA obtained above contains a nucleotide sequence of cDNA fragment obtained by SST (or consensus sequence thereof), it will be thought that the cDNA encodes signal peptide. So it is clear that the cDNA will be full-length or almost full. (All signal sequences exist at N-termini of a protein and are encoded at 5'-temini of open reading frame of cDNA.)

The confirmation may be carried out by Northern analysis with the said cDNA as a probe. It is thought that the cDNA is almost complete length, if length of the cDNA is almost the same length of the mRNA obtained in the hybridizing band.

Once the nucleotide sequences shown in SEQ ID NOs. 2, 3, 6 or 7 are determined, DNAs of the invention are obtained by chemical synthesis, or by hybridization making use of nucleotide fragments which are chemically synthesized as a probe. Furthermore, DNAs of the invention are obtained in desired amount by transforming a vector that contains the DNA into a proper host, and culturing the

transformant.

The polypeptides of the invention may be prepared by:

- (1) isolating and purifying from an organism or a cultured cell,
- (2) chemically synthesizing, or
- (3) using recombinant DNA technology,

preferably, by the method described in (3) in an industrial production.

Examples of expression system (host-vector system) for producing a polypeptide by using recombinant DNA technology are the expression systems of bacteria, yeast, insect cells and mammalian cells.

In the expression of the polypeptide, for example, in *E. coli*, the expression vector is prepared by adding the initiation codon (ATG) to 5' end of a DNA encoding mature peptide, connecting the DNA thus obtained to the downstream of a proper promoter (e.g., trp promoter, lac promoter, λ PL promoter, T7 promoter etc.), and then inserting it into a vector (e.g., pBR322, pUC18, pUC19 etc.) which functions in an *E. coli* strain.

Then, an *E. coli* strain (e.g., *E. coli* DH1 strain, *E. coli* JM109 strain, *E. coli* HB101 strain, etc.) which is transformed with the expression vector described above may be cultured in a appropriate medium to obtain the desired polypeptide. When a signal peptide of bacteria (e.g., signal peptide of pel B) is utilized, the desired polypeptide may be also released in periplasm. Furthermore, a fusion protein with other polypeptide may be also produced easily.

In the expression of the polypeptide, for example, in a mammalian cells, for example, the expression vector is prepared by inserting the DNA encoding nucleotide shown in SEQ ID NO. 3 or 7 into the downstream of a proper promoter (e.g.,

SV40 promoter, LTR promoter, metallothionein promoter etc.) in a proper vector (e.g., retrovirus vector, papilloma virus vector, vaccinia virus vector, SV40 vector, etc.). A proper mammalian cell (e.g., monkey COS-7 cell, Chinese hamster CHO cell, mouse L cell etc.) is transformed with the expression vector thus obtained, and then the transformant is cultured in a proper medium to get a desired polypeptide on the cell membrane. A vector described above can be inserted with deletion mutant DNA that encodes sequence, which is deleted transmembrane region from SEQ ID NOs. 3 or 7 and the expression vector can be transfected into an appropriate mammalian cell. The aimed soluble protein can be secreted into the culture medium. The polypeptide available by the way described above can be isolated and purified by conventional biochemical method.

Effect of the Invention

The polypeptide OAF065s of the invention show significant homology with a series of proteins which belong to TNF receptor family. Proteins, which belong to TNF receptor family, are type-1 membrane protein which have 3 to 6 repeated structure containing 6 Cys residues in the extracellular domain. It has been apparent that the proteins are related to proliferation, differentiation cell death of various cells by the interaction with ligand thereof (Craig A. Smith et. al., Cell, 76, 959-962, 1994) .

For instance, Neuronal growth factor (NGF) receptor / NGF are essential for keeping several kinds of neuronal cells surviving, allowing neuronal tubes to elongate and promoting to make neuronal transmitters (Chao M.V., J. Neurobiol., 25, 1373-1385, 1994) . Fas/FasL is essential for maintaining homeostasis in vivo,

such as destruction of cancer cells and removal of auto-reactive lymphocytes via its apoptosis-inducing activity, and also relates to CD4-positive T cell reduction in AIDS, fulminant hepatitis, graft versus host disease (GVHD) after transplantation and the onset of various autoimmune diseases (Nagata S. et. al., Science, 267, 1449-1456, 1995). CD40/CD40L is essential for activating B cells (acceleration of growth and antibody production) via T/B cell interaction (Banchereau J. et. al., Annu. Rev. Immunol., 12, 881-922, 1994). TNF receptor/TNF and lymphotoxin (LT) receptor/LT have activities, such as growth, activation and differentiation induction of various immune and hematopoietic cells, cytotoxicity and growth inhibition of tumor cells, growth and activation of various connective tissues (e.g., endothelial cells, fibroblasts, osteoblasts, etc.) and viral growth inhibition, and are also essential for the morphology or organ formation of lymphoid tissue (Ware C.F. et al., Curr. Topics Microbiol. Immunol., 198, 175-218, 1995).

Since repetitive structures of Cys are present at three points in the extracellular domain of the polypeptide of the invention, it is obvious that this is a novel protein belonging to the TNF receptor family and exerts its activity via a ligand belonging to a known or unknown TNF family. In consequence, it is considered that the polypeptide of the invention will show biological activities concerning differentiation, proliferation, growth, survival or cell death of hematopoietic, immune and nerve system cells, concerning immune system functions, concerning proliferation and growth of tumor, concerning inflammations, concerning bone metabolism.

The polypeptide of the invention is suspected to have following functions by itself or interaction with its ligands or receptors or association with other

molecules. For example, proliferation or cell death of B cells, T cells and/or mast cells or class specific induction of B cells by promotion of class switch of immunoglobulin genes; differentiation of B cells to antibody-forming cells; proliferation, differentiation, or cell death of precursors of granulocytes; proliferation, differentiation, or cell death of precursors of monocytes-macrophages; proliferation, or up regulation or cell death of neutrophils, monocytes-macrophages, eosinophils and/or basophils; proliferation, or cell death of precursors of megakaryocytes; proliferation, differentiation, or cell death of precursors of neutrophils; proliferation, differentiation, or cell death of precursors of T cells and B cells; promotion of production of erythrocytes; sustainment of proliferation of erythrocytes, neutrophils, eosinophils, basophils, monocytes-macrophages, mast cells, precursors of megakaryocyte ; promotion of migration of neutrophils, monocytes-macrophages, B cells and/or T cells; proliferation or cell death of thymocytes; suppression of differentiation of adipocytes; proliferation or cell death of natural killer cells; proliferation or cell death of hematopoietic stem cells; suppression of proliferation of stem cells and each hematopoietic precursor cells; promotion of differentiation from mesenchymal stem cells to osteoblasts or chondrocytes, proliferation or cell death of mesenchymal stem cells, osteoblasts or chondrocytes and promotion of bone absorption by activation of osteoclasts and promotion of differentiation from monocytes to osteoclasts.

This peptide is also suspected to function to nervous system, so expected to have functions below; differentiation to kinds of neurotransmitter-responsive neurons, survival or cell death of these cells; promotion of proliferation or cell

death of glial cells; spread of neural dendrites; survival or cell death of gangliocytes; proliferation, promotion of differentiation, or cell death of astrocytes; proliferation or survival of peripheral neurons; proliferation or cell death of Schwann cells; proliferation, survival or cell death of motoneurons.

Furthermore, in the process of development of early embryonic, this polypeptide is expected to promote or inhibit the organogenesis of epidermis, brain, backbone, and nervous system by induction of ectoderm, that of notochord connective tissues(bone, muscle, tendon), hemocytes, heart, kidney, and genital organs by induction of mesoderm, and that of digestive apparatus (stomach, intestine, liver, pancreas), respiratory apparatus (lung, trachea) by induction of endoderm. In adult, also, this polypeptide is thought to proliferate or inhibit the above organs.

It is known that many family of TNF receptor are expressed as soluble receptor in living body. It also known that soluble receptor inhibits its ligand by binding and trapping. So extracellular domain peptide of the invention itself works as an inhibitor is obvious.

Therefore, this polypeptide itself is expected to be used as an agent for the prevention or treatment of disease of progression or suppression of immune, nervous, or bone metabolic function, hypoplasia or overgrowth of hematopoietic cells: inflammatory disease (rheumatism, ulcerative colitis, etc.), decrease of hematopoietic stem cells after bone marrow transplantation, decrease of leukocytes, platelets, B-cells, or T-cells after radiation exposure or chemotherapeutic dosage against cancer or leukemia, anemia, infectious disease, cancer, leukemia, AIDS, bone metabolic disease(osteoporosis etc.), various degenerative disease (Alzheimer's disease, multiple sclerosis, etc.), or nervous lesion.

In addition, since this polypeptide is thought to induce the differentiation or growth of organs derived from ectoderm, mesoderm, and endoderm, this polypeptide is expected to be an agent for tissue repair (epidermis, bone, muscle, tendon, heart, kidney, stomach, intestine, liver, pancreas, lung, and trachea, etc.).

Quantitation of the polypeptide of the invention in the body can be performed using polyclonal or monoclonal antibodies against the polypeptide of the invention. It can be used the study of relationship between this polypeptide and disease or diagnosis of disease, and so on. Polyclonal and monoclonal antibodies can be prepared using this polypeptide or its fragment as an antigen by conventional methods.

Identification, purification or molecular cloning of known or unknown proteins which bind the polypeptide of the invention (preferably polypeptide of extracellular domain) can be performed using the polypeptide of the invention by, for example, preparation of the affinity-column.

Identification of the downstream signal transmission molecules which interact with the polypeptide of the invention in cytoplasm and molecular cloning of the gene can be performed:

by west-western method using the polypeptide of the invention (preferably polypeptide of transmembrane region or intracellular domain) or

by yeast two-hybrid system using the cDNA (preferably cDNA encoding transmembrane region or cytoplasmic domain of the polypeptide).

Agonists/antagonists of this receptor polypeptide and inhibitors between receptor and signal transduction molecules can be screened using the polypeptide

of the invention.

cDNAs of the invention are useful not only the important and essential template for the production of the polypeptide of the invention which is expected to be largely useful, but also be useful for diagnosis or therapy (for example, treatment of gene lacking, treatment to stop the expression of the polypeptide by antisense DNA (RNA)). Genomic DNA may be isolated with the cDNA of the invention, as a probe. As the same manner, a human gene encoding which can be highly homologous to the cDNA of the invention, that is, which encodes a polypeptide highly homologous to the polypeptide of the invention and a gene of animals excluding mouse which can be highly homologous to the cDNA of the invention, also may be isolated.

Application to Medicaments

The polypeptide of the invention or the antibody specific for the polypeptide of the invention is administered systemically or topically and in general orally or parenterally for preventing or treating diseases related to incomplete growth or abnormal growth of hematopoietic system cells, acceleration or reduction of nerve system functions or acceleration or reduction of immune system functions, such as inflammatory diseases (e.g., rheumatoid, ulcerative colitis, etc.), cytopenia of hematopoietic stem cells after bone marrow transplantation, cytopenia of leukocytes, platelets, B cells or T cells after radiation treatment or after administration of a chemotherapeutic agent, anemia, infectious diseases, cancer, leukemia, AIDS, and various degenerative diseases (e.g., Alzheimer's disease, multiple sclerosis, etc.), or nerve damage, for preventing or treating metabolic disorder of bones (e.g., osteoporosis, etc.), or for repairing tissues.

Oral administration, intravenous injection and intraventricular administration are preferred.

The doses to be administered depend upon age, body weight, symptom, desired therapeutic effect, route of administration, and duration of the treatment etc. In human adults, one dose per person is generally between 100 μ g and 100 mg, by oral administration, up to several times per day, and between 10 μ g and 100 mg, by parenteral administration up to several times per day.

As mentioned above, the doses to be used depend upon various conditions. Therefore, there are cases in which doses lower than or greater than the ranges specified above may be used.

The compounds of the invention, may be administered as solid compositions, liquid compositions or other compositions for oral administration, as injections, liniments or suppositories etc. for parenteral administration.

Solid compositions for oral administration include compressed tablets, pills, capsules, dispersible powders, granules. Capsules include soft or hard capsules.

In such compositions, one or more of the active compound(s) is or are admixed with at least one inert diluent (such as lactose, mannitol, glucose, hydroxypropyl cellulose, microcrystalline cellulose, starch, polyvinylpyrrolidone, magnesium metasilicate aluminate, etc.). The compositions may also comprise, as is normal practice, additional substances other than inert diluents: e.g. lubricating agents (such as magnesium stearate etc.), disintegrating agents (such as cellulose calcium glycolate, etc.), stabilizing agents (such as human serum albumin, lactose etc.), and assisting agents for

dissolving (such as arginine, asparaginic acid etc.).

The tablets or pills may, if desired, be coated with a film of gastric or enteric materials (such as sugar, gelatin, hydroxypropyl cellulose or hydroxypropylmethyl cellulose phthalate, etc.), or be coated with more than two films. And then, coating may include containment within capsules of absorbable materials such as gelatin.

Liquid compositions for oral administration include pharmaceutically-acceptable emulsions, solutions, syrups and elixirs. In such compositions, one or more of the active compound(s) is or are contained in inert diluent(s) commonly used (purified water, ethanol etc.). Besides inert diluents, such compositions may also comprise adjuvants (such as wetting agents, suspending agents, etc.), sweetening agents, flavoring agents, perfuming agents, and preserving agents.

Other compositions for oral administration include spray compositions which may be prepared by known methods and which comprise one or more of the active compound(s). Spray compositions may comprise additional substances other than inert diluents: e.g. stabilizing agents (sodium sulfite etc.), isotonic buffer (sodium chloride, sodium citrate, citric acid, etc.). For preparation of such spray compositions, for example, the method described in the United States Patent No. 2,868,691 or 3,095,355 (herein incorporated in their entireties by reference) may be used.

Injections for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions and emulsions. In such compositions, one or more active compound(s) is or are admixed with at least one inert aqueous diluent(s) (distilled water for injection, physiological salt solution, etc.) or inert

non-aqueous diluents(s)(propylene glycol, polyethylene glycol, olive oil, ethanol, POLYSOLBATE 80 TM , etc.).

Injectons may comprise additional compound other than inert diluents: e.g. preserving agents, wetting agents, emulsifying agents, dispersing agents, stabilizing agent (such as human serum albumin, lactose, etc.), and assisting agents such as assisting agents for dissolving (arginine, asparaginic acid, etc.).

Examples

The invention are illustrated by the following examples, but not limit the invention.

Example

Total RNA was prepared from human bone marrow stromal cell line HAS303 (provided from Professor Keisuke Sotoyama, Dr. Makoto Aizawa, first medicine, Tokyo Medical College; See J. Cell. Physiol., 148 : 245-251 (1991) and Experimental Hematol., 22 : 482-487(1994)) by TRIzol reagent (Trade Mark, GIBCOBRL). Poly(A)RNA was purified from the total RNA by mRNA purification kit (commercial name, Pharmacia).

Double strand cDNA was synthesized by SuperScript Plasmid System for cDNA Synthesis and Plasmid Cloning (brand name, GIBCOBRL) with above poly(A)RNA as template and random 9mer as primer which was containing XhoI site:

SEQ ID NO. 9

5'-CGA TTG AAT TCT AGA CCT GCC TCG AGN NNN NNN NN-3'

cDNA was ligated EcoRI adapter by DNA ligation kit ver.2 (trade name, Takara

Shuzo; this kit was used in all ligating steps hereafter.) and digested by XhoI. cDNAs were separated by agarose-gel electrophoresis. 300 - 800 bp cDNAs were isolated and were ligated to EcoRI/NotI site of pSUC2 (see US 5,536,637). E. Coli DH10B strain were transformed by pSUC2 with electroporation to obtain yeast SST cDNA library.

Plasmids of the cDNA library were prepared. Yeast YTK12 strain were transformed by the plasmids with lithium acetate method (Current Protocols In Molecular Biology 13.7.1). The transformed yeast were plated on triptphan-free medium (CMD-Try medium) for selection. The plate was incubated for 48 hour at 30 °C. Replica of the colony which is obtained by Accutran Replica Plater (trade name, Schleicher & Schuell) were place YPR plate containing raffinose for carbon source, and the plate was incubated for 14 days at 30 °C.

After 3 days, each colony appeared was streaked on YPR plate again. The plates were incubated for 48 hours at 30 °C. Single colony was inoculated to YPR medium and was incubated for 48 hours at 30 °C. Then plasmids were prepared. Insert cDNA was amplified by PCR with two kind primers which exist end side of cloning site on pSUC2 (sense strand primers were biotinylated). Biotinylated single strand of cDNAs were purified with Dynabeads (trade name, DYNAL) and determined the nucleotide sequences.

Sequencing was performed by Dye Terminator Cycle Sequencing Ready Reaction with DNA Sequencing kit (trade name, Applied Biosystems Inc.) and sequence was determined by DNA sequencer 373 (Applied Biosystems Inc.). All sequencing hereafter was carried with this method.

The clone named OAF065 is not registered on databases by homology search

of nucleotide sequence and deduced amino acid sequence and so it is cleared that the sequence is novel one. We confirmed that OAF065 contains signal peptide in view of function and structure, by comparison with known peptide which has signal peptide and deduced amino acid sequence. Full length cDNA of OAF065 was isolated by 3'-RACE(Rapid Amplification of cDNA End). Marathon cDNA Amplification Kit(trade name, Clontech) was used in 3'-RACE.

Adaptor-ligated double stranded cDNA was prepared from poly(A)RNA of HAS303 in line with the method of the kit. OAF065 specific primer F3 (28mer):
SEQ ID NO. 10

5'-AGA AAG ATG GCT TTA AAA GTG CTA CTA G-3'

which included a deduced initiation ATG codon region based on the information of nucleotide sequence by SST was prepared. PCR was performed with the said primer and adapter primer attached in the kit. Two kinds of cDNAs (4.0 kb and 1.5 kb) were amplified and 4.0 kb-cDNA was named OAF065 α and 1.5 kb-cDNA was named OAF065 β .

Two kinds cDNAs were separated with agarose-gel electrophoresis, and to pT7 Blue-2 T-Vector (trade name, Novagen), ligated in and transformed to E. Coli DH5 α and then plasmid was prepared. Nucleotide sequences of 5'-end were determined, and the existence of nucleotide sequence OAF065 specific primer F3 were confirmed in both nucleotide sequences. 5'-End nucleotide sequence (ca 1.7 kb) of OAF065 α and full length nucleotide sequence of OAF065 β were determined and then obtained sequences shown in SEQ ID NOs 3 and 7. Open reading frame was searched and deduced amino acid sequences shown in SEQ ID NO. 1 and 5 were obtained.

Compared with the nucleotide sequences of OAF065 α and OAF065 β , nucleotide sequences from 1 to 1290 base were completely same, but sequences downstream from

1291 base had no homology each other. Compared with amino acid sequences of OAF065 α and OAF065 β , amino acids from 1 to 415 in N-termini were completely same, only two amino acids in C-termini of OAF065 α were replaced to 8 amino acids (Val Arg Gln Arg Leu Gly Ser Leu) in the sequence of OAF065 α . It was revealed that OAF065 α and OAF065 β were novel type-I membrane proteins by hydrophobisity analysis and that the extracellular region and the transmembrane region of both sequences were consistant.

The polypeptide OAF065 α and OAF065 β of the invention are not known one, when amino acid sequences of the polypeptide was compared by a computer to all known sequences in data base of Swiss Prot Release 33. Extracellular Cys rich region which commonly exists in the TNF receptor family was identified in the polypeptide of the invention.

That is, compared with amino acid sequences of the polypeptide of the invention (OAF065s) and other members of TNF receptor family i.e. human necrosis factor receptor 1 (hTNFR1), human necrosis factor receptor 2 (hTNFR2), human nerve growth factor receptor (hNGFR), and human Fas (hFas), it was revealed that the polypeptides (OAF065s) of the invention are type-I membrane protein and they have extracellular Cys rich region which commonly exists in the TNF (Tumor necrosis factor) receptor family in Fig. 1.

Therefore, it was confirmed that the polypeptides OAF065 α and OAF065 β of the invention are novel membrane proteins which belong to the TNF receptor family.

SEQUENCE LIST

SEQ ID NO.: 1

Length: 417 amino acid

Type: amino acid

Topology: linear

Molecule type: protein

Sequence

Met Ala Leu Lys Val Leu Leu Glu Gln Glu Lys Thr Phe Phe Thr Leu

1 5 10 15

Leu Val Leu Leu Gly Tyr Leu Ser Cys Lys Val Thr Cys Glu Thr Gly

20 25 30

Asp Cys Arg Gln Gln Glu Phe Arg Asp Arg Ser Gly Asn Cys Val Pro

35 40 45

Cys Asn Gln Cys Gly Pro Gly Met Glu Leu Ser Lys Glu Cys Gly Phe

50 55 60

Gly Tyr Gly Glu Asp Ala Gln Cys Val Thr Cys Arg Leu His Arg Phe

65 70 75 80

Lys Glu Asp Trp Gly Phe Gln Lys Cys Lys Pro Cys Leu Asp Cys Ala

85 90 95

Val Val Asn Arg Phe Gln Lys Ala Asn Cys Ser Ala Thr Ser Asp Ala

100 105 110

Ile Cys Gly Asp Cys Leu Pro Gly Phe Tyr Arg Lys Thr Lys Leu Val

115 120 125

Gly Phe Gln Asp Met Glu Cys Val Pro Cys Gly Asp Pro Pro Pro Pro

130	135	140	
Tyr Glu Pro His Cys Ala Ser Lys Val Asn Leu Val Lys Ile Ala Ser			
145	150	155	160
Thr Ala Ser Ser Pro Arg Asp Thr Ala Leu Ala Ala Val Ile Cys Ser			
	165	170	175
Ala Leu Ala Thr Val Leu Leu Ala Leu Leu Ile Leu Cys Val Ile Tyr			
180	185	190	
Cys Lys Arg Gln Phe Met Glu Lys Lys Pro Ser Trp Ser Leu Arg Ser			
195	200	205	
Gln Asp Ile Gln Tyr Asn Gly Ser Glu Leu Ser Cys Leu Asp Pro Arg			
210	215	220	
Gln Leu His Glu Tyr Ala His Arg Ala Cys Cys Gln Cys Arg Arg Asp			
225	230	235	240
Ser Val Gln Thr Cys Gly Pro Val Arg Leu Leu Pro Ser Met Cys Cys			
	245	250	255
Glu Glu Ala Cys Ser Pro Asn Pro Ala Thr Leu Gly Cys Gly Val His			
260	265	270	
Ser Ala Ala Ser Leu Gln Ala Arg Asn Ala Gly Pro Ala Gly Glu Met			
275	280	285	
Val Pro Thr Phe Phe Gly Ser Leu Thr Gln Ser Ile Cys Gly Glu Phe			
290	295	300	
Ser Asp Ala Trp Pro Leu Met Gln Asn Pro Met Gly Gly Asp Asn Ile			
305	310	315	320
Ser Phe Cys Asp Ser Tyr Pro Glu Leu Thr Gly Glu Asp Ile His Ser			

325 330 335
 Leu Asn Pro Glu Leu Glu Ser Ser Thr Ser Leu Asp Ser Asn Ser Ser
 340 345 350
 Gln Asp Leu Val Gly Gly Ala Val Pro Val Gln Ser His Ser Glu Asn
 355 360 365

Phe Thr Ala Ala Thr Asp Leu Ser Arg Tyr Asn Asn Thr Leu Val Glu
 370 375 380
 Ser Ala Ser Thr Gln Asp Ala Leu Thr Met Arg Ser Gln Leu Asp Gln
 385 390 395 400
 Glu Ser Gly Ala Ile Ile His Pro Ala Thr Gln Thr Ser Leu Gln Glu
 405 410 415

Ala

SEQ ID NO.: 2
 Length: 1269 base pairs
 Type: nucleic acid
 Strandness: single
 Topology: linear
 Molecule type: cDNA to mRNA

Sequence

ATGGCTTTAA AAGTGCTACT AGAACAAGAG AAAACGTTTT TCACTCTTTT AGTATTACTA 60
 GGCTATTTGT CATGTAAAGT GACTTGTGAA ACAGGAGACT GTAGACAGCA AGAATTCAGG 120
 GATCGGTCTG GAAACTGTGT TCCCTGCAAC CAGTGTGGGC CAGGCATGGA GTTGTCTAAG 180

GAATGTGGCT TCGGCTATGG GGAGGATGCA CAGTGTGTGA CGTGCCGGCT GCACAGGTTC 240
 AAGGAGGACT GGGGCTTCCA GAAATGCAAG CCCTGTCTGG ACTGCGCAGT GGTGAACCGC 300
 TTTCAGAAGG CAAATTGTTC AGCCACCAGT GATGCCATCT GCGGGGACTG CTTGCCAGGA 360
 TTTTATAGGA AGACGAAACT TGTCGGCTTT CAAGACATGG AGTGTGTGCC TTGTGGAGAC 420
 CCTCCTCCTC CTTACGAACC GCACTGTGCC AGCAAGGTCA ACCTCGTGAA GATCGCGTCC 480
 ACGGCCTCCA GCCCACGGGA CACGGCGCTG GCTGCCGTTA TCTGCAGCGC TCTGGCCACC 540
 GTCCTGCTGG CCCTGCTCAT CCTCTGTGTC ATCTATTGTA AGAGACAGTT TATGGAGAAG 600
 AAACCCAGCT GGTCTCTGCG GTCACAGGAC ATTCAGTACA ACGGCTCTGA GCTGTCGTGT 660
 CTTGACAGAC CTCAGCTCCA CGAATATGCC CACAGAGCCT GCTGCCAGTG CCGCCGTGAC 720
 TCAGTGCAGA CCTGCGGGCC GGTGCGCTTG CTCCCATCCA TGTGCTGTGA GGAGGCCTGC 780
 AGCCCCAACC CGGCGACTCT TGGTTGTGGG GTGCATTCTG CAGCCAGTCT TCAGGCAAGA 840
 AACGCAGGCC CAGCCGGGGA GATGGTGCCG ACTTTCTTCG GATCCCTCAC GCAGTCCATC 900
 TGTGGCGAGT TTTCAGATGC CTGGCCTCTG ATGCAGAATC CCATGGGTGG TGACAACATC 960
 TCTTTTTGTG ACTCTTATCC TGAAC TCACT GGAGAAGACA TTCATTCTCT CAATCCAGAA 1020
 CTTGAAAGCT CAACGTCTTT GGATTCAAAT AGCAGTCAAG ATTTGGTTGG TGGGGCTGTT 1080
 CCAGTCCAGT CTCATTCTGA AAAC TTTACA GCAGCTACTG ATTTATCTAG ATATAACAAC 1140
 AACTGGTAG AATCAGCATC AACTCAGGAT GCACTAACTA TGAGAAGCCA GCTAGATCAG 1200
 GAGAGTGGCG CTATCATCCA CCCAGCCACT CAGACGTCCC TCCAGGTAAG GCAGCGACTG 1260
 GGTTCCTG 1269

SEQ ID NO.: 3

length: 1704 base pairs

Type: nucleic acid

Strandness: single

Topology: linear

Molecule type: cDNA to mRNA

Sequence

GGGAACGTAG AACTCTCCAA CAATAAATAC ATTTGATAAG AAAGATGGCT TTAAAAGTGC 60
TACTAGAACA AGAGAAAACG TTTTTCACCTC TTTTAGTATT ACTAGGCTAT TTGTCATGTA 120
AAGTGACTTG TGAAACAGGA GACTGTAGAC AGCAAGAATT CAGGGATCGG TCTGGAAACT 180
GTGTTCCCTG CAACCAGTGT GGGCCAGGCA TGGAGTTGTC TAAGGAATGT GGCTTCGGCT 240
ATGGGGAGGA TGCACAGTGT GTGACGTGCC GGCTGCACAG GTTCAAGGAG GACTGGGGCT 300
TCCAGAAATG CAAGCCCTGT CTGGACTGCG CAGTGGTGAA CCGCTTTCAG AAGGCAAATT 360
GTTTCAGCCAC CAGTGATGCC ATCTGCGGGG ACTGCTTGCC AGGATTTTAT AGGAAGACGA 420
AACTTGTCGG CTTTCAAGAC ATGGAGTGTG TGCCTTGTGG AGACCCTCCT CCTCCTTACG 480
AACCGBACTG TGCCAGCAAG GTCAACCTCG TGAAGATCGC GTCCACGGCC TCCAGCCCAC 540
GGGACACGGC GCTGGCTGCC GTTATCTGCA GCGCTCTGGC CACCGTCCTG CTGGCCCTGC 600
TCATCCTCTG TGTCATCTAT TGTAAGAGAC AGTTTATGGA GAAGAAACCC AGCTGGTCTC 660
TGCGGTCACA GGACATTCAG TACAACGGCT CTGAGCTGTC GTGTCTTGAC AGACCTCAGC 720
TCCACGAATA TGCCACAGA GCCTGCTGCC AGTGCCGCCG TGA CTGAGTGCAG CAGACCTGCG 780
GGCCGGTGCG CTTGCTCCCA TCCATGTGCT GTGAGGAGGC CTGCAGCCCC AACCCGGCGA 840
CTCTTGATTG TGGGGTGCAT TCTGCAGCCA GTCTTCAGGC AAGAAACGCA GGCCAGCCG 900
GGGAGATGGT GCCGACTTTC TTCGGATCCC TCACGCAGTC CATCTGTGGC GAGTTTTTCAG 960
ATGCCTGGCC TCTGATGCAG AATCCCATGG GTGGTGACAA CATCTCTTTT TGTGACTCTT 1020
ATCCTGAACT CACTGGAGAA GACATTCATT CTCTCAATCC AGAACTTGAA AGCTCAACGT 1080
CTTTGGATTG AAATAGCAGT CAAGATTGTTG TTGGTGGGGC TGTTCCAGTC CAGTCTCATT 1140
CTGAAAACCTT TACAGCAGCT ACTGATTTAT CTAGATATAA CAACACACTG GTAGAATCAG 1200
CATCAACTCA GGATGCACTA ACTATGAGAA GCCAGCTAGA TCAGGAGAGT GGCGCTATCA 1260

TCCACCCAGC CACTCAGACG TCCCTCCAGG AAGCTTAAAG AACCTGCTTC TTTCTGCAGT 1320
 AGAAGCGTGT GCTGGAACCC AAAGAGTACT CCTTTGTTAG GCTTATGGAC TGAGCAGTCT 1380
 GGACCTTGCA TGGCTTCTGG GGCAAAAATA AATCTGAACC AAACCTGACGG CATTTGAAGC 1440
 CTTTCAGCCA GTTGCTTCTG AGCCAGACCA GCTGTAAGCT GAAACCTCAA TGAATAACAA 1500
 GAAAAGACTC CAGGCCGACT CATGATACTC TGCATCTTTC CTACATGAGA AGCTTCTCTG 1560
 CCACAAAAGT GACTTCAAAG ACGGATGGGT TGAGCTGGCA GCCTATGAGA TTGTGGACAT 1620
 ATAACAAGAA ACAGAAATGC CCTCATGCTT ATTTTCATGG TGATTGTGGT TTTACAAGAC 1680
 TGAAGACCCA GAGTATACTT TTTC 1704

SEQ ID NO.: 4

Length: 1704 base pairs

Type: nucleic acid

Strandness: single

Topology: linear

Molecule type: cDNA to mRNA

Original source:

Organism: Homo Sapiens

Cell line: HAS303

Feature

Name/Key: CDS

Location: 45..1295

Identification method: P

Name/Key: sig peptide

Location: 45..119

Identification method: S

Name/Key: mat peptide

Location: 120..1295

Identification method: S

Sequecne

GGGAACGTAG AACTCTCCAA CAATAAATAC ATTTGATAAG AAAG ATG GCT TTA AAA 56

Met Ala Leu Lys

-25

GTG CTA CTA GAA CAA GAG AAA ACG TTT TTC ACT CTT TTA GTA TTA CTA 104

Val Leu Leu Glu Gln Glu Lys Thr Phe Phe Thr Leu Leu Val Leu Leu

-20

-15

-10

GGC TAT TTG TCA TGT AAA GTG ACT TGT GAA ACA GGA GAC TGT AGA CAG 152

Gly Tyr Leu Ser Cys Lys Val Thr Cys Glu Thr Gly Asp Cys Arg Gln

-5

1

5

10

CAA GAA TTC AGG GAT CGG TCT GGA AAC TGT GTT CCC TGC AAC CAG TGT 200

Gln Glu Phe Arg Asp Arg Ser Gly Asn Cys Val Pro Cys Asn Gln Cys

15

20

25

GGG CCA GGC ATG GAG TTG TCT AAG GAA TGT GGC TTC GGC TAT GGG GAG 248

Gly Pro Gly Met Glu Leu Ser Lys Glu Cys Gly Phe Gly Tyr Gly Glu

30

35

40

GAT GCA CAG TGT GTG ACG TGC CGG CTG CAC AGG TTC AAG GAG GAC TGG 296

Asp Ala Gln Cys Val Thr Cys Arg Leu His Arg Phe Lys Glu Asp Trp

45

50

55

GGC TTC CAG AAA TGC AAG CCC TGT CTG GAC TGC GCA GTG GTG AAC CGC 344

Tyr Asn Gly Ser Glu Leu Ser Cys Leu Asp Rro Arg Gln Leu His Glu															
190				195				200							
TAT GCC CAC AGA GCC TGC TGC CAG TGC CGC CGT GAC TCA GTG CAG ACC 776															
Tyr Ala His Arg Ala Cys Cys Gln Cys Arg Arg Asp Ser Val Gln Thr															
205				210				215							
TGC GGG CCG GTG CGC TTG CTC CCA TCC ATG TGC TGT GAG GAG GCC TGC 824															
Cys Gly Pro Val Arg Leu Leu Pro Ser Met Cys Cys Glu Glu Ala Cys															
220				225				230				235			
AGC CCC AAC CCG GCG ACT CTT GGT TGT GGG GTG CAT TCT GCA GCC AGT 872															
Ser Pro Asn Pro Ala Thr Leu Gly Cys Gly Val His Ser Ala Ala Ser															
240				245				250							
CTT CAG GCA AGA AAC GCA GGC CCA GCC GGG GAG ATG GTG CCG ACT TTC 920															
Leu Gln Ala Arg Asn Ala Gly Pro Ala Gly Glu Met Val Pro Thr Phe															
255				260				265							
TTC GGA TCC CTC ACG CAG TCC ATC TGT GGC GAG TTT TCA GAT GCC TGG 968															
Phe Gly Ser Leu Thr Gln Ser Ile Cys Gly Glu Phe Ser Asp Ala Trp															
270				275				280							
CCT CTG ATG CAG AAT CCC ATG GGT GGT GAC AAC ATC TCT TTT TGT GAC 1016															
Pro Leu Met Gln Asn Pro Met Gly Gly Asp Asn Ile Ser Phe Cys Asp															
285				290				295							
TCT TAT CCT GAA CTC ACT GGA GAA GAC ATT CAT TCT CTC AAT CCA GAA 1064															
Ser Tyr Pro Glu Leu Thr Gly Glu Asp Ile His Ser Leu Asn Pro Glu															
300				305				310				315			
CTT GAA AGC TCA ACG TCT TTG GAT TCA AAT AGC AGT CAA GAT TTG GTT 1112															

Leu Glu Ser Ser Thr Ser Leu Asp Ser Asn Ser Ser Gln Asp Leu Val

320

325

330

GGT GGG GCT GTT CCA GTC CAG TCT CAT TCT GAA AAC TTT ACA GCA GCT 1160

Gly Gly Ala Val Pro Val Gln Ser His Ser Glu Asn Phe Thr Ala Ala

335

340

345

ACT GAT TTA TCT AGA TAT AAC AAC ACA CTG GTA GAA TCA GCA TCA ACT 1208

Thr Asp Leu Ser Arg Tyr Asn Asn Thr Leu Val Glu Ser Ala Ser Thr

350

355

360

CAG GAT GCA CTA ACT ATG AGA AGC CAG CTA GAT CAG GAG AGT GGC GCT 1256

Gln Asp Ala Leu Thr Met Arg Ser Gln Leu Asp Gln Glu Ser Gly Ala

365

370

375

ATC ATC CAC CCA GCC ACT CAG ACG TCC CTC CAG GAA GCT TAAAGAACCT 1305

Ile Ile His Pro Ala Thr Gln Thr Ser Leu Gln Glu Ala

380

385

390

GCTTCTTTCT GCAGTAGAAG CGTGTGCTGG AACCCAAAGA GTACTCCTTT GTTAGGCTTA 1365

TGGACTGAGC AGTCTGGACC TTGCATGGCT TCTGGGGCAA AAATAAATCT GAACCAAACCT 1425

GACGGCATTG GAAGCCTTTC AGCCAGTTGC TTCTGAGCCA GACCAGCTGT AAGCTGAAAC 1485

CTCAATGAAT AACAAGAAAA GACTCCAGGC CGACTCATGA TACTCTGCAT CTTTCCTACA 1545

TGAGAAGCTT CTCTGCCACA AAAGTGACTT CAAAGACGGA TGGGTTGAGC TGGCAGCCTA 1605

TGAGATTGTG GACATATAAC AAGAAACAGA AATGCCCTCA TGCTTATTTT CATGGTGATT 1665

GTGGTTTTAC AAGACTGAAG ACCCAGAGTA TACTTTTTTC 1704

SEQ ID NO.: 5

Length: 423 amino acids

Type: amino acid

Topology: linear

Molecule type: protein

Sequence

Met Ala Leu Lys Val Leu Leu Glu Gln Glu Lys Thr Phe Phe Thr Leu
1 5 10 15
Leu Val Leu Leu Gly Tyr Leu Ser Cys Lys Val Thr Cys Glu Thr Gly
20 25 30
Asp Cys Arg Gln Gln Glu Phe Arg Asp Arg Ser Gly Asn Cys Val Pro
35 40 45
Cys Asn Gln Cys Gly Pro Gly Met Glu Leu Ser Lys Glu Cys Gly Phe
50 55 60
Gly Tyr Gly Glu Asp Ala Gln Cys Val Thr Cys Arg Leu His Arg Phe
65 70 75 80
Lys Glu Asp Trp Gly Phe Gln Lys Cys Lys Pro Cys Leu Asp Cys Ala
85 90 95
Val Val Asn Arg Phe Gln Lys Ala Asn Cys Ser Ala Thr Ser Asp Ala
100 105 110
Ile Cys Gly Asp Cys Leu Pro Gly Phe Tyr Arg Lys Thr Lys Leu Val
115 120 125
Gly Phe Gln Asp Met Glu Cys Val Pro Cys Gly Asp Pro Pro Pro Pro
130 135 140
Tyr Glu Pro His Cys Ala Ser Lys Val Asn Leu Val Lys Ile Ala Ser
145 150 155 160

Thr	Ala	Ser	Ser	Pro	Arg	Asp	Thr	Ala	Leu	Ala	Ala	Val	Ile	Cys	Ser
				165					170					175	
Ala	Leu	Ala	Thr	Val	Leu	Leu	Ala	Leu	Leu	Ile	Leu	Cys	Val	Ile	Tyr
				180					185					190	
Cys	Lys	Arg	Gln	Phe	Met	Glu	Lys	Lys	Pro	Ser	Trp	Ser	Leu	Arg	Ser
				195					200					205	
Gln	Asp	Ile	Gln	Tyr	Asn	Gly	Ser	Glu	Leu	Ser	Cys	Leu	Asp	Pro	Arg
		210					215						220		
Gln	Leu	His	Glu	Tyr	Ala	His	Arg	Ala	Cys	Cys	Gln	Cys	Arg	Arg	Asp
225					230					235				240	
Ser	Val	Gln	Thr	Cys	Gly	Pro	Val	Arg	Leu	Leu	Pro	Ser	Met	Cys	Cys
				245					250					255	
Glu	Glu	Ala	Cys	Ser	Pro	Asn	Pro	Ala	Thr	Leu	Gly	Cys	Gly	Val	His
			260					265						270	
Ser	Ala	Ala	Ser	Leu	Gln	Ala	Arg	Asn	Ala	Gly	Pro	Ala	Gly	Glu	Met
			275					280						285	
Val	Pro	Thr	Phe	Phe	Gly	Ser	Leu	Thr	Gln	Ser	Ile	Cys	Gly	Glu	Phe
		290					295							300	
Ser	Asp	Ala	Trp	Pro	Leu	Met	Gln	Asn	Pro	Met	Gly	Gly	Asp	Asn	Ile
305					310					315				320	
Ser	Phe	Cys	Asp	Ser	Tyr	Pro	Glu	Leu	Thr	Gly	Glu	Asp	Ile	His	Ser
				325						330				335	
Leu	Asn	Pro	Glu	Leu	Glu	Ser	Ser	Thr	Ser	Leu	Asp	Ser	Asn	Ser	Ser
			340						345					350	

Gln Asp Leu Val Gly Gly Ala Val Pro Val Gln Ser His Ser Glu Asn

355

360

365

Phe Thr Ala Ala Thr Asp Leu Ser Arg Tyr Asn Asn Thr Leu Val Glu

370

375

380

Ser Ala Ser Thr Gln Asp Ala Leu Thr Met Arg Ser Gln Leu Asp Gln

385

390

395

400

Glu Ser Gly Ala Ile Ile His Pro Ala Thr Gln Thr Ser Leu Gln Val

405

410

415

Arg Gln Arg Leu Gly Ser Leu

420

SEQ ID NO.: 6

Length: 1269 base pairs

Type: nucleic acid

Strandness: single

Topology: linear

Molecule type: cDNA to mRNA

Sequecne

```
ATGGCTTTAA AAGTGCTACT AGAACAAGAG AAAACGTTTT TCACTCTTTT AGTATTACTA 60
GGCTATTTGT CATGTAAAGT GACTTGTGAA ACAGGAGACT GTAGACAGCA AGAATTCAGG 120
GATCGGTCTG GAAACTGTGT TCCCTGCAAC CAGTGTGGGC CAGGCATGGA GTTGTCTAAG 180
GAATGTGGCT TCGGCTATGG GGAGGATGCA CAGTGTGTGA CGTGCCGGCT GCACAGGTTC 240
AAGGAGGACT GGGGCTTCCA GAAATGCAAG CCCTGTCTGG ACTGCGCAGT GGTGAACCGC 300
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TTTCAGAAGG CAAATTGTTC AGCCACCAGT GATGCCATCT GCGGGGACTG CTTGCCAGGA 360
TTTTATAGGA AGACGAAACT TGTGGGCTTT CAAGACATGG AGTGTGTGCC TTGTGGAGAC 420
CCTCCTCCTC CTTACGAACC GCACTGTGCC AGCAAGGTCA ACCTCGTGAA GATCGCGTCC 480
ACGGCCTCCA GCCCACGGGA CACGGCGCTG GCTGCCGTTA TCTGCAGCGC TCTGGCCACC 540
GTCCTGCTGG CCCTGCTCAT CCTCTGTGTC ATCTATTGTA AGAGACAGTT TATGGAGAAG 600
AAACCCAGCT GGTCTCTGCG GTCACAGGAC ATTCAGTACA ACGGCTCTGA GCTGTCGTGT 660
CTTGACAGAC CTCAGCTCCA CGAATATGCC CACAGAGCCT GCTGCCAGTG CCGCCGTGAC 720
TCAGTGCAGA CCTGCGGGCC GGTGCGCTTG CTCCCATCCA TGTGCTGTGA GGAGGCCTGC 780
AGCCCCAACC CGGCGACTCT TGGTTGTGGG GTGCATTCTG CAGCCAGTCT TCAGGCAAGA 840
AACGCAGGCC CAGCCGGGGA GATGGTGCCG ACTTTCTTCG GATCCCTCAC GCAGTCCATC 900
TGTGGCGAGT TTTCAGATGC CTGGCCTCTG ATGCAGAATC CCATGGGTGG TGACAACATC 960
TCTTTTGTG ACTCTTATCC TGAACTCACT GGAGAAGACA TTCATTCTCT CAATCCAGAA 1020
CTTGAAAGCT CAACGTCTTT GGATTCAAAT AGCAGTCAAG ATTTGGTTGG TGGGGCTGTT 1080
CCAGTCCAGT CTCATTCTGA AAACCTTACA GCAGCTACTG ATTTATCTAG ATATAACAAC 1140
ACACTGGTAG AATCAGCATC AACTCAGGAT GCACTAACTA TGAGAAGCCA GCTAGATCAG 1200
GAGAGTGGCG CTATCATCCA CCCAGCCACT CAGACGTCCC TCCAGGTAAG GCAGCGACTG 1260
GGTTCCTG

```

1269

```

SEQ ID NO.:      7
Length:          1496 base pairs
Type:            nucleic acid
Strandness:      single
Topology:         linear
Molecule type:  cDNA to mRNA

```

Sequence

GGGAACGTAG AACTCTCCAA CAATAAATAC ATTTGATAAG AAAGATGGCT TAAAAAGTGC 60
TACTAGAACA AGAGAAAACG TTTTTCACCTC TTTTAGTATT ACTAGGCTAT TTGTCATGTA 120
AAGTGAATTG TGAAACAGGA GACTGTAGAC AGCAAGAATT CAGGGATCGG TCTGGAAACT 180
GTGTTCCCTG CAACCAGTGT GGGCCAGGCA TGGAGTTGTC TAAGGAATGT GGCTTCGGCT 240
ATGGGGAGGA TGCACAGTGT GTGACGTGCC GGCTGCACAG GTTCAAGGAG GACTGGGGCT 300
TCCAGAAATG CAAGCCCTGT CTGGACTGCG CAGTGGTGAA CCGCTTTCAG AAGGCAAATT 360
GTTCAGCCAC CAGTGATGCC ATCTGCGGGG ACTGCTTGCC AGGATTTTAT AGGAAGACGA 420
AACTTGTCGG CTTTCAAGAC ATGGAGTGTG TGCCTTGTGG AGACCCTCCT CTCCTTACG 480
AACCGCACTG TGCCAGCAAG GTCAACCTCG TGAAGATCGC GTCCACGGCC TCCAGCCCAC 540
GGGACACGGC GCTGGCTGCC GTTATCTGCA GCGCTCTGGC CACCGTCCTG CTGGCCCTGC 600
TCATCCTCTG TGTCATCTAT TGTAAGAGAC AGTTTATGGA GAAGAAACCC AGCTGGTCTC 660
TGCGGTCACA GGACATTCAG TACAACGGCT CTGAGCTGTC GTGTCTTGAC AGACCTCAGC 720
TCCACGAATA TGCCACAGA GCCTGCTGCC AGTGCCGCCG TGAATCAGT CAGACCTGCG 780
GGCCGGTGCG CTTGCTCCCA TCCATGTGCT GTGAGGAGGC CTGCAGCCCC AACCCGGCGA 840
CTCTTGTTG TGCGGTGAT TCTGCAGCCA GTCTTCAGGC AAGAAACGCA GGCCAGCCG 900
GGGAGATGGT GCCGACTTTC TTCGGATCCC TCACGCAGTC CATCTGTGGC GAGTTTTTCTC 960
ATGCCTGGCC TCTGATGCAG AATCCCATGG GTGGTGACAA CATCTCTTTT TGTGACTCTT 1020
ATCCTGAACT CACTGGAGAA GACATTCATT CTCTCAATCC AGAACTTGAA AGCTCAACGT 1080
CTTTGGATTC AAATAGCAGT CAAGATTTGG TTGGTGGGGC TGTTCCAGTC CAGTCTCATT 1140
CTGAAAACCT TACAGCAGCT ACTGATTTAT CTAGATATAA CAACACACTG GTAGAATCAG 1200
CATCAACTCA GGATGCACTA ACTATGAGAA GCCAGCTAGA TCAGGAGAGT GGCGCTATCA 1260
TCCACCCAGC CACTCAGACG TCCCTCCAGG TAAGGCAGCG ACTGGGTTCC CTGTGAACAC 1320
AGCACTGACT TACAGTAGAT CAGAACTCTG TTCCAGCAT AAGATTTGGG GGAACCTGAT 1380

GAGTTTTTTT TTTGCATCTT TAATAATTC TTGTATGTTG TAGAGTATGT TTAAAAATAA 1440
ATTCAAGTA TTTTTTTTAA AACTAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAA 1496

SEQ ID NO.: 8
Length: 1496 base pairs
Type: nucleic acid
Strandness: single
Topology: linear
Molecule type: cDNA to mRNA
Original source

Organism: Homo Sapiens

Cell line: HAS303

Feature

Name/Key: CDS
Location: 45..1313
Identification method: P
Name/Key: sig peptide
Location: 45..119
Identification method: S
Name/Key: mat peptide
Location: 120..1313
Identification method: S

Sequence

GGGAACGTAG AACTCTCCAA CAATAAATAC ATTTGATAAG AAAG ATG GCT TTA AAA 56

Met Ala Leu Lys

-25

GTG CTA CTA GAA CAA GAG AAA ACG TTT TTC ACT CTT TTA GTA TTA CTA 104
Val Leu Leu Glu Gln Glu Lys Thr Phe Phe Thr Leu Leu Val Leu Leu

-20

-15

-10

GGC TAT TTG TCA TGT AAA GTG ACT TGT GAA ACA GGA GAC TGT AGA CAG 152
Gly Tyr Leu Ser Cys Lys Val Thr Cys Glu Thr Gly Asp Cys Arg Gln

-5

1

5

10

CAA GAA TTC AGG GAT CGG TCT GGA AAC TGT GTT CCC TGC AAC CAG TGT 200
Gln Glu Phe Arg Asp Arg Ser Gly Asn Cys Val Pro Cys Asn Gln Cys

15

20

25

GGG CCA GGC ATG GAG TTG TCT AAG GAA TGT GGC TTC GGC TAT GGG GAG 248
Gly Pro Gly Met Glu Leu Ser Lys Glu Cys Gly Phe Gly Tyr Gly Glu

30

35

40

GAT GCA CAG TGT GTG ACG TGC CGG CTG CAC AGG TTC AAG GAG GAC TGG 296
Asp Ala Gln Cys Val Thr Cys Arg Leu His Arg Phe Lys Glu Asp Trp

45

50

55

GGC TTC CAG AAA TGC AAG CCC TGT CTG GAC TGC GCA GTG GTG AAC CGC 344
Gly Phe Gln Lys Cys Lys Pro Cys Leu Asp Cys Ala Val Val Asn Arg

60

65

70

75

TTT CAG AAG GCA AAT TGT TCA GCC ACC AGT GAT GCC ATC TGC GGG GAC 392
Phe Gln Lys Ala Asn Cys Ser Ala Thr Ser Asp Ala Ile Cys Gly Asp

80

85

90

TGC TTG CCA GGA TTT TAT AGG AAG ACG AAA CTT GTC GGC TTT CAA GAC 440

Cys Leu Pro Gly Phe Tyr Arg Lys Thr Lys Leu Val Gly Phe Gln Asp												
95				100				105				
ATG GAG TGT GTG CCT TGT GGA GAC CCT CCT CCT CCT TAC GAA CCG CAC												488
Met Glu Cys Val Pro Cys Gly Asp Pro Pro Pro Pro Tyr Glu Pro His												
110				115				120				
TGT GCC AGC AAG GTC AAC CTC GTG AAG ATC GCG TCC ACG GCC TCC AGC												536
Cys Ala Ser Lys Val Asn Leu Val Lys Ile Ala Ser Thr Ala Ser Ser												
125				130				135				
CCA CGG GAC ACG GCG CTG GCT GCC GTT ATC TGC AGC GCT CTG GCC ACC												584
Pro Arg Asp Thr Ala Leu Ala Ala Val Ile Cys Ser Ala Leu Ala Thr												
140				145				150				155
GTC CTG CTG GCC CTG CTC ATC CTC TGT GTC ATC TAT TGT AAG AGA CAG												632
Val Leu Leu Ala Leu Leu Ile Leu Cys Val Ile Tyr Cys Lys Arg Gln												
160				165				170				
TTT ATG GAG AAG AAA CCC AGC TGG TCT CTG CGG TCA CAG GAC ATT CAG												680
Phe Met Glu Lys Lys Pro Ser Trp Ser Leu Arg Ser Gln Asp Ile Gln												
175				180				185				
TAC AAC GGC TCT GAG CTG TCG TGT CTT GAC AGA CCT CAG CTC CAC GAA												728
Tyr Asn Gly Ser Glu Leu Ser Cys Leu Asp Rro Arg Gln Leu His Glu												
190				195				200				
TAT GCC CAC AGA GCC TGC TGC CAG TGC CGC CGT GAC TCA GTG CAG ACC												776
Tyr Ala His Arg Ala Cys Cys Gln Cys Arg Arg Asp Ser Val Gln Thr												
205				210				215				
TGC GGG CCG GTG CGC TTG CTC CCA TCC ATG TGC TGT GAG GAG GCC TGC												824

Cys Gly Pro Val Arg Leu Leu Pro Ser Met Cys Cys Glu Glu Ala Cys																
220		225		230		235										
AGC	CCC	AAC	CCG	GCG	ACT	CTT	GGT	TGT	GGG	GTG	CAT	TCT	GCA	GCC	AGT	872
Ser Pro Asn Pro Ala Thr Leu Gly Cys Gly Val His Ser Ala Ala Ser																
		240				245							250			
CTT	CAG	GCA	AGA	AAC	GCA	GGC	CCA	GCC	GGG	GAG	ATG	GTG	CCG	ACT	TTC	920
Leu Gln Ala Arg Asn Ala Gly Pro Ala Gly Glu Met Val Pro Thr Phe																
		255				260							265			
TTC	GGA	TCC	CTC	ACG	CAG	TCC	ATC	TGT	GGC	GAG	TTT	TCA	GAT	GCC	TGG	968
Phe Gly Ser Leu Thr Gln Ser Ile Cys Gly Glu Phe Ser Asp Ala Trp																
		270				275							280			
CCT	CTG	ATG	CAG	AAT	CCC	ATG	GGT	GGT	GAC	AAC	ATC	TCT	TTT	TGT	GAC	1016
Pro Leu Met Gln Asn Pro Met Gly Gly Asp Asn Ile Ser Phe Cys Asp																
		285				290							295			
TCT	TAT	CCT	GAA	CTC	ACT	GGA	GAA	GAC	ATT	CAT	TCT	CTC	AAT	CCA	GAA	1064
Ser Tyr Pro Glu Leu Thr Gly Glu Asp Ile His Ser Leu Asn Pro Glu																
300			305					310						315		
CTT	GAA	AGC	TCA	ACG	TCT	TTG	GAT	TCA	AAT	AGC	AGT	CAA	GAT	TTG	GTT	1112
Leu Glu Ser Ser Thr Ser Leu Asp Ser Asn Ser Ser Gln Asp Leu Val																
			320					325						330		
GGT	GGG	GCT	GTT	CCA	GTC	CAG	TCT	CAT	TCT	GAA	AAC	TTT	ACA	GCA	GCT	1160
Gly Gly Ala Val Pro Val Gln Ser His Ser Glu Asn Phe Thr Ala Ala																
		335						340						345		
ACT	GAT	TTA	TCT	AGA	TAT	AAC	AAC	ACA	CTG	GTA	GAA	TCA	GCA	TCA	ACT	1208

Thr Asp Leu Ser Arg Tyr Asn Asn Thr Leu Val Glu Ser Ala Ser Thr
 350 355 360
 CAG GAT GCA CTA ACT ATG AGA AGC CAG CTA GAT CAG GAG AGT GGC GCT 1256
 Gln Asp Ala Leu Thr Met Arg Ser Gln Leu Asp Gln Glu Ser Gly Ala
 365 370 375
 ATC ATC CAC CCA GCC ACT CAG ACG TCC CTC CAG GTA AGG CAG CGA CTG 1304
 Ile Ile His Pro Ala Thr Gln Thr Ser Leu Gln Val Arg Gln Arg Leu
 380 385 390 395
 GGT TCC CTG TGAACACAG CACTGACTTA CAGTAGATCA GAACTCTGTT CCCAGCATAA 1362
 Gly Ser Leu
 GATTGGGGG AACCTGATGA GTTTTTTTTT TGCATCTTTA ATAATTTCTT GTATGTTGTA 1422
 GAGTATGTTT TAAATAAAT TTCAAGTATT TTTTTTAAAA ACTAAAAAAA AAAAAAAAAA 1482
 AAAAAAAAAA AAAA 1496

Brief Description of the Drawing

Fig. 1 shows comparison of the amino acid sequence of the invention and that of TNF receptor family. hTNFR1 represents human necrosis factor receptor 1, hTNFR2 represents human necrosis factor receptor 2, hNGFR represents human nerve growth factor receptor, and hFas represents human Fas, in this figure.

Fig. 1

OAF065	1	-----	MALKVLLEQE	KTFF--TLLV	LLGYLSCKVT	CETGDCRQQE	38
hTNFR1	1	-MGLSTVPDL	LLPLVLLELL	VGIYPSGVIG	LVPHLGDREK	RDSV-CPQ GK	48
hTNFR2	1	----MAPVAV	WAALAVGLEL	WAAA--HALP	AQVAFTPYAP	EPGSTCRLRE	44
hNGFR	1	-----	--MGAGATGR	AMDG--PRL	LLLLLGVSLG	GAKEACPTGL	36
hFas	1	MLGIWTLPL	VLTSVARLSS	KSVN--AQVT	DINSKGLELR	KTVTTVETQN	48
OAF065	39	FRDRSGNCVP	CNQ-CGPGME	LSKECGFGYG	EDAQCVTCL	HR-FK-EDWG	85
hTNFR1	49	YIHPQNNSIC	CTK-CHKGT	LYNDGP-GPG	QDTDCRECES	GS-FTASENH	95
hTNFR2	45	YYDQTAQ-MC	CSK-CSPGQH	AKVFC--TKT	SDTVCDSCED	ST-YT-QLWN	88
hNGFR	37	Y-THSGEC--	CKA-CNLGEG	VAQPCGANQT	VCEPCLD-SV	TF-SD-VVSA	79
hFas	49	LEGLHHDGQF	CHKPCPPGER	KARDCTVN-G	DEPDCVPCQE	GKEYT-DKAH	96
OAF065	86	F-QCKPCPLD	-CAVVRNFQ-	KANCSATSDA	ICGDCPLPGFY	...	122
hTNFR1	96	L-RHCLSCSK	-CRKEMGQVE	ISSCTVDRDT	VCG-CRKNQY	...	132
hTNFR2	89	WVPECLSCGS	RCSSDQVE--	TQACTREQNR	IC-TCRPGWY	...	125
hNGFR	80	T-EPCKPCTE	-CVGLQSM--	SAPCVEADDA	VC-RCAYGY	...	114
hFas	97	FSSKCRRCRL	-CDEGHGLEV	EINCTRTQNT	KC-RCKPNFF	...	134

Document Name: Abstract

Abstract

Constitution

Polypeptide produced from human stromal cell line, the process for the preparation of the polypeptide, DNA encoding the polypeptide, vector carrying the DNA, host cell transformed by the vector, antibody of the polypeptide, and pharmaceutical composition containing the polypeptide or the antibody.

Effect

It is considered that the polypeptide of the invention will show biological activities concerning differentiation, proliferation, growth, survival or cell death of hematopoietic, immune and nerve system cells, concerning immune system functions, concerning proliferation and growth of tumor, concerning inflammations, concerning bone metabolism. Therefore, the polypeptide of the invention is expected to be used as an agent for the prevention or treatment of disease of progression or suppression of immune, nervous, or bone metabolic function, hypoplasia or overgrowth of hematopoietic cells

Figure selected: None